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P01/7700 0.00-0020842.1

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PCS10942WMD-PROV

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Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

THERAPEUTIC COMPOSITIONS

2 Applicant's details

0020842.1

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(if known) 06892673001

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

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Forenames

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3
An address for service in the United Kingdom must be supplied.
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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [] ➡ *go to 3b*

⬇ ***Please give details below***

Agent's name
W. M. DADSON
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number 07750136001

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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Daytime telephone number*(if available)*

ADP number
(if known)

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10942WMD-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

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☐ filing date *(day month year)*

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, or
- any applicant is a corporate body.

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

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You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

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A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	3	Description	9
Abstract	1	Drawing(s)	

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9 Request

I/~~We~~ request the grant of a patent on the basis of this application.

Signed W.M. Dawson Date 23/08/2000
(day month year)

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THERAPEUTIC COMPOSITIONS

The present invention is concerned with pharmaceutical compositions comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

Amlodipine is a well-known calcium channel-blocking agent which is used in the treatment of hypertension and angina. Amlodipine is a dihydropyridine with an assymetric centre at the 4-position; presently, amlodipine is only approved for administration in the form of the racemate, specifically that of the besylate salt.

The individual enantiomers of amlodipine have been isolated (*J Med Chem* 1986 29 1696, Arrowsmith *et al*) and identified as R(+) and S(-) (*J Med Chem* 1992 35 3341-3344, Goldmann *et al*). The calcium channel-blocking activity of the racemate has been found to reside largely, but not exclusively, in the S(-) enantiomer *(J Cardiovasc Pharmacol* 12 (Supp 6) S144, J W Rigby *et al)*.

European Patent No. 0754043 describes the surprising ability of the R(+) enantiomer of amlodipine to inhibit PDGF-induced vascular smooth muscle cell migration using an *in vitro* system which effect may prove to be useful in the treatment of conditions such as atherosclerosis, restenosis after angioplasty and endometriosis.

It has now been found that the R(+) enantiomer of amlodipine has another unexpected property, specifically the ability to release NO, a potent vasodilator and inhibitor of platelet aggregation and the active species in nitroglycerin (*Kidney International* 49 S2-S5 1996, Ignarro), from endothelial and vascular smooth muscle cells (hereinafter referred to as "vascular NO").

When amlodipine is administered as the racemate, the NO-induced cardiovascular effects of the R(+) enantiomer are largely 'masked' by the potent anti-hypertensive effects of the S(-) enantiomer. Furthermore, the amount of racemate which may safely be administered is limited by the hypotensive activity of the S(-) enantiomer which, in excess of about 0.5 mg/kg, can give rise to adverse effects such as a marked and sustained fall in blood pressure and reduced coronary blood flow. The R(+) enantiomer, on the other hand, is expected to provide beneficial cardiovascular effects at concentrations far exceeding those at which the S(-) enantiomer begins to produce unwanted effects. Thus using the racemate of amlodipine places an artificial limit on the amount of R(+) enantiomer which may be administered and deprives the patient of the full cardiovascular benefits of said enantiomer.

The problem which the present invention seeks to address is to provide amlodipine compositions comprising sufficient S(-) enantiomer to achieve the

with a preservative, such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment, such as petrolatum.

For topical application to the skin, the composition of the invention may be formulated as a suitable ointment containing the active material suspended or dissolved in, for example, a mixture comprising one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture comprising one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Finally, the compositions of the invention may be administered *via* intracavernosal injection.

The preparation of an enriched enantiomer mixture in accordance with the present invention and pharmaceutical compositions thereof is illustrated by the following Examples.

EXAMPLE 1

PREPARATION OF R(+) AMLODIPINE SALTS FROM RACEMIC AMLODIPINE BESYLATE

(1) PREPARATION OF RACEMIC AMLODIPINE FREE BASE

To a slight suspension of racemic amlodipine besylate (100.37 g, 0.177 mol) [prepared by the method described in European Patent No. 0244944] in methylene chloride (250 mL, 2.5 mL/g) and water (250 mL, 2.5 mL/g) was added 11 M sodium hydroxide (24 mL) to achieve pH 13-14. The mixture was stirred for ten minutes during which time it became a solution. The layers were separated and the organic layer washed with water (1x 250 mL) and gravity filtered through a magnesium sulphate (25 g) bed. The magnesium sulphate was washed with methylene chloride (40 mL) and to the combined filtrates was added dimethyl sulphoxide (360 mL). The methylene chloride was removed on a rotary evaporator (45 minutes on a water aspirator followed by 15 minutes under high vacuum).

(2) PREPARATION AND SEPARATION OF R(+) AMLODIPINE TARTRATE DIASTEREOISOMER

To the dimethyl sulphoxide solution of racemic amlodipine free base obtained in Step (1) was added a solution of L-tartaric acid (6.62 g, 0.044 mol, 0.25 equiv) in dimethyl sulphoxide (360 mL). The solution was stirred at ambient temperature for six hours and the resulting solid collected by suction filtration

and washed with acetone (200 mL). (Note: it is important that the dimethyl sulphoxide be completely removed from the solid before the solid is washed with acetone.) The solid was dried *in vacuo* at 50°C overnight to give (R)-amlodipine-hemi-L-tartrate-DMSO-solvate (68.25 g) as a pale yellow, tacky solid. The filtrate was set aside and may be used in the isolation of (S)-amlodipine free base.

(3) PREPARATION OF R(+) AMLODIPINE FREE BASE

To a solution of the (R)-amlodipine-hemi-L-tartrate-DMSO-solvate (68.25 g) obtained in Step (2) in methylene chloride (345 mL, 5 mL/g) was added a solution of 50% sodium hydroxide (73 mL) in water (72 mL). The solution was stirred at ambient temperature for 40 minutes. The layers were separated and the organic layer extracted with water (1 x 150 mL) and gravity filtered through a magnesium sulphate (25 g) bed. The magnesium sulphate was washed with methylene chloride (40 mL) and the methylene chloride removed on a rotary evaporator using a water aspirator. Heptane was added to the evaporation flask as the volume allowed. Eventually, all of the methylene chloride was removed and 600 mL of heptane was added to the flask. The resulting solid was collected by suction filtration, washed with heptane and dried *in vacuo* at 50°C overnight to give (R)-amlodipine free base (19.4 g, 53.4% yield) as an off-white solid.

Chemical purity by HPLC:	99.95%
Chiral purity by HPLC:	98.88%

(4) PREPARATION OF R(+) SALTS

(a) SUCCINATE

To a solution of the (R)-amlodipine free base (1.0 g, 2.45 mmol) obtained in Step (3) in ethanol (15 mL) was added succinic acid (0.29 g, 2.45 mmol) in ethanol (8 mL). The mixture was allowed to stand at ambient temperature overnight. The resulting solid was collected by suction filtration, rinsed with cold ethanol and dried *in vacuo* at 40°C overnight. An additional 6 hours *in vacuo* at 60°C gave the (R)-amlodipine succinate (1.11 g, 86.0% yield) as a white solid.

(b) MESYLATE

(R)-Amlodipine free base (1.0 g, 2.45 mmol) obtained in Step (3) was dissolved in isopropyl alcohol (23 mL) after fifteen minutes stirring at ambient temperature. Methanesulphonic acid (0.24 g, 2.45 mmol) in isopropyl alcohol (2 mL) was added and the solution stirred at ambient temperature for 3 hours. After cooling in the refrigerator overnight, a small amount of solid had formed which amount slightly increased after a further night in the freezer. The solid was collected by suction filtration, rinsed with cold isopropyl alcohol and dried

in vacuo at 40°C overnight. Drying *in vacuo* at 80°C overnight gave the (R)-amlodipine mesylate (1.08 g, 87.4% yield) as a beige solid.

EXAMPLE 2

PREPARATION OF S(-) AMLODIPINE SALTS FROM RACEMIC AMLODIPINE BESYLATE

S(-) amlodipine succinate and S(-) amlodipine mesylate may be prepared in analogous fashion using, for example, D-tartaric acid rather than L-tartaric acid in Step (2) to prepare and isolate the corresponding diastereoisomer. Alternatively, the L-tartaric disastereoisomer may be worked up from the liquors left after isolation of the R(+) diastereoisomer.

EXAMPLE 3

OPTIONAL PREPARATIONS OF ENRICHED ENANTIOMER MIXTURE

(1) To 0.5 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 was added 0.1 mole of S(-) enantiomer free base or a salt thereof prepared by a method in accordance with Example 2 and the resulting mixture homogenised.

(2) To 0.2 mole of racemic amlodipine besylate was added 0.4 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 and the resulting mixture homogenised.

(3) A solution comprising 0.5 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 and 0.1 mole of S(-) enantiomer free base or a salt thereof prepared by a method in accordance with Example 2 was allowed to crystallise and the resulting crystals filtered off.

EXAMPLE 4

SUITABLE FORMULATIONS

Tablets	
	mg/tablet
Active ingredient	24.24
Microcrystalline cellulose Ph Eur	50.00
Lactose Ph Eur	121.76
Croscarmellose sodium NF	2.00
Magnesium stearate Ph Eur	2.00

The active ingredient is sieved and blended with the other components. The resultant mix is compressed into tablets using a rotary tablet press (Manesty

Betapress) fitted with 6 mm normal concave punches. The resultant tablets may be film-coated with an appropriate film-coating material.

Capsules	
	mg/capsule
Active ingredient	18.18
Lactose Ph Eur	208.89
Maize starch Ph Eur	69.63
Colloidal anhydrous silica Ph Eur	0.30
Magnesium stearate Ph Eur	3.00
Fill weight	300.00

The active ingredient is sieved and blended with the other components. The mix is filled into Size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing the capsule size to suit.

CLAIMS

1. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an anti-hypertensive amount of the S(-) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof and a suitable excipient, diluent, or carrier, characterised in that said enantiomers are present in a ratio by weight (based on free base) of R(+) enantiomer : S(-) enantiomer of greater than 1:1.

2. A pharmaceutical composition according to Claim 1 wherein said ratio is less than 10:1.

3. A pharmaceutical composition according to Claim 1 or 2 wherein said ratio is in the range 2:1 to 8:1.

4. A pharmaceutical composition according to any of Claims 1 to 3 wherein said ratio is approximately 5:1.

5. A pharmaceutical composition according to any of Claims 1 to 4 which comprises a mixture of single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof and single crystals of the S(-) enantiomer or pharmaceutically acceptable salt thereof in the desired ratio.

6. A pharmaceutical composition according to Claim 5 wherein both enantiomers are in the form of pharmaceutically acceptable salts.

7. A pharmaceutical composition according to Claim 6 wherein the salts of both enantiomers have the same counter ion.

8. A pharmaceutical composition according to any of Claims 1 to 4 which comprises single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof and mixed crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof in the desired ratio.

9. A pharmaceutical composition according to Claims 8 wherein the mixed crystals are racemic.

10. A pharmaceutical composition according to Claims 8 and 9 wherein the R(+) enantiomer is in the form of a pharmaceutically acceptable salt and the enantiomers in the mixed crystals are also in the form of pharmaceutically acceptable salts.

11. A pharmaceutical composition according to any of Claims 8 to 10 wherein the salt of the R(+) enantiomer and the salts of the enantiomers in the mixed crystals all have the same counter ion.

12. A pharmaceutical composition according to any of Claims 1 to 4 which comprises mixed crystals containing both the R(+) enantiomer or pharmaceutically acceptable salt thereof and the S(-) enantiomer or pharmaceutically acceptable salt thereof in the desired ratio.

13. A pharmaceutical composition according to Claim 12 wherein both enantiomers are in the form of pharmaceutically acceptable salts.

14. A pharmaceutical composition according to Claim 13 wherein the salts of both enantiomers have the same counter ion.

15. A pharmaceutical composition according to any of Claims 7, 11 or 14 wherein said counter ion is mesylate or succinate.

16. A pharmaceutical composition according to any of Claims 1 to 15 which is in the form of a tablet or capsule suitable for oral administration.

17. A pharmaceutical composition according to any of Claims 1 to 15 which is in liquid dosage form.

18. A pharmaceutical composition according to any of Claim 1 to 15 which is in the form of a solution suitable for intravenous (iv) administration.

19. A process for the preparation of a composition according to any of Claims 5 to 7 wherein single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof are mixed in the desired ratio with single crystals of the S(-) enantiomer or pharmaceutically acceptable salt thereof.

20. A process for the preparation of a composition according to any of Claims 8 to 11 wherein single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof are mixed in the desired ratio with crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof.

21. A process for the preparation of a composition according to any of Claims 12 to 14 wherein mixed crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof in the desired ratio are formed by co-crystallisation.

22. The R(+) enantiomer of amlodipine or a pharmaceutically acceptable salt thereof for use in the treatment of a condition for which a vascular NO-releasing agent is indicated.

23. A pharmaceutical composition according to any of Claims 1 to 18 for use in the treatment of a condition for which a vascular NO-releasing agent is indicated.

24. A pharmaceutical composition according to any of Claims 1 to 18 for use in a treatment of a condition for which both an anti-hypertensive and a vascular NO-releasing agent are indicated.

25. The use of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition for which a vascular NO-releasing agent is indicated.

26. The use of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition for which both an anti-hypertensive agent and a vascular NO-releasing agent are indicated.

27. Use according to Claim 25 or 26 wherein said medicament is a pharmaceutical composition in accordance with any of Claims 1 to 18.

28. A method of treating a condition for which a vascular NO-releasing agent is indicated which comprises the administration of a composition in accordance with any of Claims 1 to 18.

29. A method of treating a condition for which both an anti-hypertensive agent and a vascular NO-releasing agent are indicated which comprises the administration of a composition in accordance with any of Claims 1 to 18.

30. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an NO-inducing amount of an ACE inhibitor and a suitable excipient, diluent, or carrier.

31. A composition according to Claim 30 wherein said ACE inhibitor is ramaprilat or quinapril.

32. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an NO-potentiating amount of a PDE_5 inhibitor and a suitable excipient, diluent, or carrier.

33. A composition according to Claim 32 wherein said PDE_5 inhibitor is sildenafil.

ABSTRACT

THERAPEUTIC COMPOSITIONS

The present invention is concerned with pharmaceutical compositions comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

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